REMARKS/ARGUMENTS

Claims 66-71, 73-75 and 77-86 are active in this case. Claims 84 and 86 have been withdrawn from consideration by the Office and are so indicated in the listing of claims.

Claims 75 and 83 are amended to remove "bone marrow stromal cells" as a mesenchymal cell. Therefore, Applicants now elect chondrocytes as the mesenchymal cell species according to the previous Restriction imposed by the Office. This was discussed during the meeting noted below and it is understood that this change in election is acceptable to the Examiner.

Claim 66 is amended to clarify that the cultured cells are mature, which finds support in the specification on page 7, lines 6-7.

The specification is amended to provide a substitute title as requested.

Formal drawings are being filed herewith to correct the deficiency noted by the Examiner on page 3 of the Office Action.

No new matter is added.

The issue under 37 CFR 1.75 and the rejection of claim 72 under 35 USC 112, second paragraph are not longer applicable in light of the amendments submitted herein.

Applicants thank the Examiner for the courtesy of discussing this case with the Applicants' undersigned representative on March 9, 2006. During this discussion, it was noted that a Declaration of Alan Smith, one of the named inventors of the present application and an author on the Smith et al Abstract cited in the rejection on page 7 would be provided. Following that discussion, a signed Declaration is attached. As attested to by Mr. Smith in his Declaration, authors Gorgas, Jensen, Hatle and Brott were working under the direction and supervision of the named inventors of this application. Therefore, as the Smith et al publication is not a disclosure by another, and Smith et al is part of the basis for the rejection under 35 USC 103(a), Applicants request that this rejection be withdrawn.

As further basis to withdraw the rejection, it should be noted that both US '126 and US '994 relate to the culturing of stem and/or progenitor cells and the cultures are optimized for that purpose. In contrast, the culturing conditions employed in the claimed methods are optimized to obtain mature human cells with enhanced biological function that are then used in therapeutic applications.

Regarding the new matter rejection under 35 USC 112, first paragraph, as outlined in the Office Action and as reiterated during the above-noted meeting, it is the Examiner's position that there is inadequate support for transferring cultured cells to generate issue or for any other therapeutic benefit. For the reasons explained during the meeting and outlined again below, the specification unquestionably supports the claimed methods.

First, it should be noted that the claims, as amended herein, are to providing therapeutic benefit.

The application text describes cell culturing, transferring cells for therapeutic applications (referring to page 21-22 of the specification) and that among others, therapeutic applications include tissue repair (pages 5-6) and the development and regeneration of tissue (referring to page 11, first paragraph of the specification). As discussed in the specification on pages 5-6 of the application, the invention is based on the Inventors' discovery that culturing mature cells in the manner defined in the claims allows one to obtain cells that have significant capabilities in proliferating *ex vivo* and the cells obtained also have higher biological function, i.e., are more potent cells. Because the cells which are cultured according to the conditions claimed are more potent, these cells have a far greater capacity to be used in therapeutic applications wherever such cells are used, including adoptive therapies, wound healing, burn care, organ repair, and others as listed in the specification. There cannot be any dispute about the fact that the specification clearly states that the cultured cells can be

used for therapeutic benefits. In fact, in the section bridging pages 21-22 of the specification, it is specifically stated that the cells, after culturing, are harvested and infused into a patient to provide a therapeutic benefit, including generating tissue (see page 6 of the specification). What more could be disclosed?

In fact, the Examiner has already recognized that the specification discloses the ability to provide therapeutic benefits including tissue generation (non-elected claim) as stated on page 10 of the Action. In the obviousness-type double patenting rejection based on a sister application (which has issued into US patent no. 6,835,566) and therefore has the same specification, the Examiner recognized that "it would be immediately obvious to one skill in the art that the referenced cell with enhanced biological function includes the ability to generate tissue." (page 10, last paragraph of the Office Action).

Assuming the Examiner maintains that a particular phrase, *per se*, is not explicitly recited in the specification, Applicants note that the Board of Patent Appeals and Interferences (BPAI) has overturned a rejection made under 35 U.S.C. § 112, first paragraph where the Examiner rejected claims on the grounds that the claim expressions did not appear in the original disclosure (In re Sorenson 3 USPQ2d 1462 (BPAI 1987)). In this case, the terms "binuclear copper complexes of carboxylic acids", "binuclear copper complex of an aliphatic carboxylic acid" and "a binuclear copper complex of an arylcarboxylic acid" were held not to violate 35 U.S.C. § 112, first paragraph in view of the fact that the specification contained four examples of binuclear cooper complexes of carboxylic acids and one example of a binuclear copper complex of an aliphatic carboxylic acid. "Given those working examples together with a broader disclosure of copper complexes of carboxylic acids, both aliphatic and aromatic, we have no doubt that the Applicants' disclosure *reasonably conveys to the skilled artisan that Appellant had possession of the subject matter now claimed*." Id. at

1464 (italics added). In dicta the BPAI stated "we are mindful that Appellants' specification need not describe the claimed invention in *ipsis verbus* to comply with a written description requirement" Id. at 1463, and "the test is whether the originally filed specification disclosure *reasonably* conveys to a person having ordinary skill that Applicant had possession of the subject matter later claimed." Id. at 1464 citing to In re Kaslow 217 U.S.P.Q. 1089 (CAFC 1983).

Applicants submit that the decision in Sorenson is relevant to the present rejection in that the specification clearly discusses obtaining more potent cells according to the culturing protocol and using those cells for providing therapeutic benefits to human patients. Therefore, the claims presented in this application do not represent new matter and were described in the original specification in such a way as to reasonably convey to one of ordinary skill in the art that Applicants had possession of the claimed invention. Withdrawal of this rejection is requested.

The last item discussed during the above-noted meeting was the rejection under 35 USC 112, first paragraph based on the allegation that the claims are not enabled. As discussed above in the context of the new matter rejection, the invention is based on the Inventors' discovery that culturing mature cells in the manner defined in the claims allows one to obtain cells that have significant capabilities in proliferating *ex vivo* and the cells obtained also have higher biological function, i.e., are more potent cells (referring to pages 5-6 of the specification). Because the cells which are cultured according to the conditions claimed are more potent, these cells have a far greater capacity to be used in therapeutic applications wherever such cells are used. In other words, there is a body of evidence that is known in the art of using mature cells for therapeutic purposes. The inventors have discovered a way to make these cells better and more potent for such therapeutic applications.

Some examples of such uses of mature cells from the literature are summarized below with PubMed abstracts attached for further reference. While some of these articles were published after the effective filing date of the present application, they demonstrate the effectiveness of the methodologies specifically described in the specification.

A sampling of articles includes:

Mansoor W et al (Br J Cancer. 2005 Nov 14;93(10):1085-91) discusses the uses and benefits of T-cell therapies.

Banchereau J. (Transfus Sci. 1997 Jun;18(2):313-26) discusses the use and benefits of using dendritic cells for therapy.

Irintchev A et al (J Physiol. 1997 May 1;500 (Pt 3):775-85) discusses using primary myoblasts to improve muscle function.

Baums MH et al (J Bone Joint Surg Am. 2006 Feb;88(2):303-8) discusses chondrocyte transplantation for treating cartilage defects.

Baltzer AW, Arnold JP (Arthroscopy. 2005 Feb;21(2):159-66) discusses benefits and approaches for bone and cartilage cell transplantation.

Dorotka R et al (Z Rheumatol. 2004 Oct;63(5):385-92) discusses the success of autologous chondrocyte transplantation in knee and ankle therapeutic applications.

Giannini S et al (Foot Ankle Int. 2001 Jun;22(6):513-7) also describes autologous chondrocyte transplantation in osteochondral lesions of the ankle joint.

Micheli LJ et al (Clin J Sport Med. 2001 Oct;11(4):223-8) describe "excellent graft survivorship using ACI as well as substantial improvement in functional outcome."

Musgrave DS et al (Clin Orthop Relat Res. 2000 Sep;(378):290-305) discusses the potential of different cell types to produce bone tissue.

Chubinskaya S, Kuettner KE. (Int J Biochem Cell Biol. 2003 Sep;35(9):1323-40) reviews the potential of chondrocytes to regulate osteogenesis.

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In fact, as discussed above in relation to the new matter rejection, the Examiner has already recognized that recognized that "it would be immediately obvious to one skill in the art that the referenced cell with enhanced biological function includes the ability to generate tissue." (page 10, last paragraph of the Office Action, noting the specification of US patent no. 6,835,566 is identical to the specification of the present application).

In view of the above, Applicants request that this ground of rejection be withdrawn.

Applicants request that the rejection under the doctrine of obviousness type double patenting in view of co-pending application no. 09/027,671 be held in abeyance since the alleged conflicting claims have not yet been patented (see MPEP § 822.01).

With respect to the same basis of rejection in view of the sister application, now U.S. patent no. 6,835,566, a terminal disclaimer is attached. Withdrawal of the rejection is requested.

Finally, a Notice of Allowance indicating all claims have been allowed is requested.

Respectfully submitted,

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Related Articles, Links

1: Br J Cancer. 2005 Nov 14;93(10):1085-91.

Engineering T cells for cancer therapy.

Mansoor W, Gilham DE, Thistlethwaite FC, Hawkins RE.

Cancer Research UK, Department of Medical Oncology, University of Manchester, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Withington, Manchester, UK.

It is generally accepted that the immune system plays an important role in controlling tumour development. However, the interplay between tumour and immune system is complex, as demonstrated by the fact that tumours can successfully establish and develop despite the presence of T cells in tumour. An improved understanding of how tumours evade T-cell surveillance, coupled with technical developments allowing the culture and manipulation of T cells, has driven the exploration of therapeutic strategies based on the adoptive transfer of tumour-specific T cells. The isolation, expansion and re-infusion of large numbers of tumour-specific T cells generated from tumour biopsies has been shown to be feasible. Indeed, impressive clinical responses have been documented in melanoma patients treated with these T cells. These studies and others demonstrate the potential of T cells for the adoptive therapy of cancer. However, the significant technical issues relating to the production of natural tumour-specific T cells suggest that the application of this approach is likely to be limited at the moment. With the advent of retroviral gene transfer technology, it has become possible to efficiently endow T cells with antigen-specific receptors. Using this strategy, it is potentially possible to generate large numbers of tumour reactive T cells rapidly. This review summarises the current gene therapy approaches in relation to the development of adoptive T-cell-based cancer treatments, as these methods now head towards testing in the clinical trial setting.

Publication Types:
- Review

PMID: 16251873 [PubMed - indexed for MEDLINE].

Related Articles, Links

1: Transfus Sci. 1997 Jun;18(2):313-26.

ELSEVIER FULL-TEXT ARTICLE

Dendritic cells: therapeutic potentials.

Banchereau J.

Schering-Plough, Laboratory for Immunological Research, Dardilly, France.

Dendritic cells (DCs) are leukocytes that are specialized to capture antigens and initiate T-cell-mediated immune responses. After capture of antigens, DCs, then in an immature stage, leave their tissue of residence and migrate through the lymph/blood into secondary lymphoid organs where they differentiate into mature cells. Because DCs can prime animals in the absence of any other adjuvant, they have been termed 'nature's adjuvant'. Large numbers of DCs can now be generated from circulating monocytes or from CD34 hematopoietic progenitors in response to GM-CSF in combination with either IL4 or TNF alpha. In mice, tumor antigen loaded DCs have been shown to prevent the development of tumors and even to induce the regression of established tumors. DCs therapy represents a very promising approach to the treatment of cancer and infectious diseases. Early studies indicate the existence of DC populations that can induce tolerance and may prove useful in organ transplantation.

Publication Types:

- Review

PMID: 10174695 [PubMed - indexed for MEDLINE]

☐ 1: J Physiol. 1997 May 1;500 (Pt 3):775-85. Related Articles, Links

Functional improvement of damaged adult mouse muscle by implantation of primary myoblasts.

Irintchev A, Langer M, Zweyer M, Theisen R, Wernig A.

Department of Physiology, University of Bonn, Germany.

1. Myoblasts from expanded primary cultures were implanted into cryodamaged soleus muscles of adult BALB/c mice. One to four months later isometric tension recordings were performed in vitro, and the male donor cells implanted into female hosts were traced on histological sections using a Y-chromosome-specific probe. The muscles were either mildly or severely cryodamaged, which led to reductions in tetanic muscle force to 33% (n = 9 muscles, 9 animals) and 70% (n = 11) of normal, respectively. Reduced forces resulted from deficits in regeneration of muscle tissue as judged from the reduced desmin-positive cross-sectional areas (34 and 66% of control, respectively). 2. Implantation of 10(6) myogenic cells into severely cryodamaged muscles more than doubled muscle tetanic force (to 70% of normal, n = 14), as well as specific force (to 66% of normal). Absolute and relative amount of desmin-positive muscle cross-sectional areas were significantly increased indicating improved microarchitecture and less fibrosis. Newly formed muscle tissue was fully innervated since the tetanic forces resulting from direct and indirect (nerve-evoked) stimulation were equal. Endplates were found on numerous Y-positive muscle fibres. 3. As judged from their position under basal laminae of muscle fibres and the expression of M-cadherin, donor-derived cells contributed to the pool of satellite cells on small- and large-diameter muscle fibres. 4. Myoblast implantation after mild cryodamage and in undamaged muscles had little or no functional or structural effects; in both preparations only a few Y-positive muscle nuclei were detected. It is concluded that myoblasts from expanded primary cultures-unlike permanent cell lines-significantly contribute to muscle regeneration only when previous muscle damage is extensive and loss of host satellite cells is severe.

PMID: 9161990 [PubMed - indexed for MEDLINE]

1: J Bone Joint Surg Am. 2006 Feb;88(2):303-8.

Autologous chondrocyte transplantation for treating cartilage defects of the talus.

Baums MH, Heidrich G, Schultz W, Steckel H, Kahl E, Klinger HM.

Departments of Orthopaedic Surgery, Georg-August University Gottingen, Robert-Koch-Strasse 40, D-37075 Gottingen, Germany. mike.baums@freenet.de

BACKGROUND: Despite its highly specialized nature, articular cartilage has a poor reparative capability. Treatment of symptomatic osteochondral defects of the talus has been especially difficult until now. METHODS: We performed autologous chondrocyte transplantation in twelve patients with a focal deep cartilage lesion of the talus. There were seven female and five male patients with a mean age of 29.7 years. The mean size of the lesion was 2.3 cm(2). All patients were studied prospectively. Evaluation was performed with use of the Hannover ankle rating score, the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot score, a visual analogue scale for pain, and magnetic resonance imaging. RESULTS: All patients were available for follow-up at a mean of sixty-three months. There was a significant improvement in the Hannover score, from 40.4 points preoperatively to 85.5 points at the follow-up examination, with seven excellent results, four good results, and one satisfactory result. The AOFAS mean score was 88.4 points compared with 43.5 points preoperatively. Magnetic resonance imaging showed a nearly congruent joint surface in seven patients, discrete irregularities in four, and an incongruent surface in one. The patients who had been involved in competitive sports were able to return to their full activity level. CONCLUSIONS: The promising clinical results of this study suggest that autologous chondrocyte transplantation is an effective and safe way to treat symptomatic osteochondral defects of the talus in appropriately selected patients.

Publication Types:

- Clinical Trial

PMID: 16452741 [PubMed - indexed for MEDLINE]

1: Arthroscopy. 2005 Feb;21(2):159-66.

Bone-cartilage transplantation from the ipsilateral knee for chondral lesions of the talus.

Baltzer AW, Arnold JP.

Center for Orthopaedic Surgery, Molecular Orthopaedics, and Neurosurgery, Dusseldorf, Germany. axel.baltzer@gmx.de

PURPOSE: We present a prospective analysis to review talus dome chondral and osteochondral lesions treated with autogenous bone-cartilage transplantation harvested from the ipsilateral knee since 1998. The clinical outcome of osteochondral defects is investigated by using a method for resurfacing that supplies hyaline cartilage. The outcome analysis also considers defect size and the number of transplanted osteochondral cylinders. TYPE OF STUDY: Prospective analysis of a case series. METHODS: Included in the study were 43 patients with ankle joint pain resulting from osteochondritis dissecans stage III-IV (n = 22), post-traumatic cartilage defects (n = 16), and focal osteoarthritis (n = 5). The mean age of this group was 31.2 years; there were 30 male and 13 female patients. To carry out the osteochondral resurfacing procedure, anteromedial or anterolateral arthrotomy (23 cases) or medial malleolar osteotomy (20 cases) of the distal tibia was performed. The osteochondral autograft transfer system (OATS; Arthrex, Naples, FL) was used for transplantation. The follow-up examinations were performed after 3 months (clinical, radiological), after 6 months (clinical, radiological), after 9 months (clinical, radiological, hardware removal, and second-look arthroscopy), after 12 months, and every following year (clinical, radiological, magnetic resonance imaging). The follow-up of 11 patients was greater than 2 years (maximum, 4.5 years), for 8 patients 1 to 2 years, for 12 patients 6 to 12 months, and for another 12 patients 0 to 6 months. The results have been validated by the scores of Evanski and Waugh score and Mazur et al. RESULTS: The mean pain intensity measured by visual analogue scale (0 to 10, with 10 representing the worst imaginable pain) reduced from 4.4 to 2.3 after 6 months (n = 34), to 1.6 after 1 year (n = 23), and after 2 years to 1.1 (n = 14). Patients reported a significantly improved range of motion of the ankle compared with their preoperative status. The smaller the diameter of the transplants and the smaller the number of transplants used, the better were the results in pain reduction and postoperative range of motion. The Evanski and Waugh score improved from 52 to 88 points and the score described by Mazur et al. from 53 to 90 of 100 possible points. All medial osteotomies were healed clinically and radiographically. All grafts showed bony integration in the

Related Articles, Links

1: Z Rheumatol. 2004 Oct;63(5):385-92.

SpringerLink FULL-TEXT ARTICLE

[Mid-term results of autologous chondrocyte transplantation in knee and ankle. A one- to six-year follow-up study]

[Article in German]

Dorotka R, Kotz R, Trattnig S, Nehrer S.

Universitatsklinik fur Orthopadie Wien, Wahringer Gurtel 18-20, 1090, Wien, Austria.

BACKGROUND: The reimplantation of autologous chondrocytes is a new technique in reconstruction of cartilage defects; initial results achieved with this technique have been promising. In an arthroscopic procedure, scales of cartilage are obtained from intact cartilage. The chondrocytes are then multiplied in special laboratories. A few weeks later, in a second procedure, the cartilage defect is filled with the cell suspension and closed with a flap of periosteum. METHOD: At our department, autologous chondrocyte transplantation (ACT) has been used in 10 patients since 1996, in 6 cases in the knee joint, and in 4 cases in the ankle joint. The mean age of the patients was 30 years. The mean size of the defect was 4 cm (2). In 4 patients, a parallel surgical procedure was required at the time of removal. RESULTS: The mean duration of follow-up was 21/2 years. Six patients had good to excellent results, 3 patients had moderate results, and one patient a poor result. The modified Cincinnati rating scale was improved from 2.4 to 7.1 points, and the Lysholm score from 59.2 to 86.6 points. The AOFAS score for ankle joints had improved from 33 to 76. CONCLUSION: We were able to show that ACT achieves improvement in the knee as well as ankle joint in the majority of patients. ACT appears to be a promising therapeutic concept for both joints.

PMID: 15517299 [PubMed - indexed for MEDLINE]

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Related Articles, Links

1: Clin J Sport Med. 2001 Oct;11(4):223-8.

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Autologous chondrocyte implantation of the knee: multicenter experience and minimum 3-year follow-up.

Micheli LJ, Browne JE, Erggelet C, Fu F, Mandelbaum B, Moseley JB, Zurakowski D.

Division of Sports Medicine, Department of Orthopaedic Surgery, Children's Hospital, and Harvard Medical School, Boston, Massachusetts 02115, USA.

OBJECTIVE: To determine clinical outcome and graft survivorship in patients undergoing autologous chondrocyte implantation (ACI) for the repair of chondral defects of the knee. DESIGN: Prospective cohort study. SETTING: 19 centers in the United States. PATIENTS: 50 patients (37 males, 13 females). Mean age was 36 years (range: 19-53). Defects were grade III or IV with a mean size of 4.2 cm 2. All patients had a minimum of 36 months postoperative follow-up. MAIN OUTCOME MEASUREMENTS: Clinician and patient evaluation based on the modified Cincinnati Knee Rating System. Graft failure was defined as replacement or removal of the graft due to mechanical symptoms or pain. RESULTS: Clinician and patient evaluation indicated median improvements of 4 and 5 points, respectively, at 36 months following ACI ($p < 0.001$). Previous treatment with marrow stimulation techniques and size of defect did not impact the results with ACI. The most common adverse events reported were adhesions and arthrofibrosis and hypertrophic changes. Three patients had graft failure and required reimplantation or treatment with alternative cartilage repair techniques. Kaplan-Meier estimated freedom from graft failure was 94% at 36 months postoperatively (95% CI = 88-100%). CONCLUSIONS: These results of this study indicate excellent graft survivorship using ACI as well as substantial improvement in functional outcome.

Publication Types:

- Clinical Trial
- Multicenter Study

PMID: 11753058 [PubMed - indexed for MEDLINE]

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1: Clin Orthop Relat Res. 2000 Sep;(378):290-305.

Ex vivo gene therapy to produce bone using different cell types.

Musgrave DS, Bosch P, Lee JY, Pelinkovic D, Ghivizzani SC, Whalen J, Niyibizi C, Huard J.

Department of Orthopaedic Surgery, University of Pittsburgh, PA, USA.

Gene therapy and tissue engineering promise to revolutionize orthopaedic surgery. This study comprehensively compares five different cell types in ex vivo gene therapy to produce bone. The cell types include a bone marrow stromal cell line, primary muscle derived cells, primary bone marrow stromal cells, primary articular chondrocytes, and primary fibroblasts. After transduction by an adenovirus encoding for bone morphogenetic protein-2, all of the cell types were capable of secreting bone morphogenetic protein-2. However, the bone marrow stromal cell line and muscle derived cells showed more responsiveness to recombinant human bone morphogenetic protein-2 than did the other cell types. In vivo injection of each of the cell populations transduced to secrete bone morphogenetic protein-2 resulted in bone formation. Radiographic and histologic analyses corroborated the in vitro data regarding bone morphogenetic protein-2 secretion and cellular osteocompetence. This study showed the feasibility of using primary bone marrow stromal cells, primary muscle derived cells, primary articular chondrocytes, primary fibroblasts, and an osteogenesis imperfecta stromal cell line in ex vivo gene therapy to produce bone. The study also showed the advantages and disadvantages inherent in using each cell type.

PMID: 10987005 [PubMed - indexed for MEDLINE]

All: 1 Review: 1

Related Articles, Links

1: Int J Biochem Cell Biol. 2003 Sep;35(9):1323-40.

ELSEVIER FULL-TEXT ARTICLE

Regulation of osteogenic proteins by chondrocytes.

Chubinskaya S, Kuettner KE.

Department of Biochemistry, Rush Medical College at Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612, USA. Schubins@rush.edu

The purpose of this review is to summarize the current scientific knowledge of bone morphogenetic proteins (BMPs) in adult articular cartilage. We specifically focus on adult cartilage, since one of the major potential applications of the members of the BMP family may be a repair of adult tissue after trauma and/or disease. After reviewing cartilage physiology and BMPs, we analyze the data on the role of recombinant BMPs as anabolic agents in tissue formation and restoration in different in vitro and in vivo models following with the endogenous expression of BMPs and factors that regulate their expression. We also discuss recent transgenic modifications of BMP genes and subsequent effect on cartilage matrix synthesis. We found that the most studied BMPs in adult articular cartilage are BMP-7 and BMP-2 as well as transforming growth factor-beta (TGF-beta). There are a number of contradicting reports for some of these growth factors, since different models, animals, doses, time points, culture conditions and devices were used. However, regardless of the experimental conditions, only BMP-7 or osteogenic protein-1 (OP-1) exhibits the most convincing effects. It is the only BMP studied thus far in adult cartilage that demonstrates strong anabolic activity in vitro and in vivo with and without serum. OP-1 stimulates the synthesis of the majority of cartilage extracellular matrix proteins in adult articular chondrocytes derived from different species and of different age. OP-1 counteracts the degenerative effect of numerous catabolic mediators; it is also expressed in adult human, bovine, rabbit and goat articular cartilage. This review reveals the importance of the exploration of the BMPs in the cartilage field and highlights their significance for clinical applications in the treatment of cartilage-related diseases.

Publication Types:
- Review

PMID: 12798347 [PubMed - indexed for MEDLINE]

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